DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: DEC 29 2003

From: Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Pre-market Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: **Creatine Ethyl Ester HCl**

Firm: ProNutrient Technologies, Inc.

Date Received by FDA: 7/11/03

90-Day Date: 10/09/03

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day pre-market notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Tanya L. Jackson

Tanya Jackson, Botanist HFD 810

95S-0316

RPT190

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, Maryland 20740

Dr. Samuel Augustine
ProNutrient Technologies, Inc.
11515 North 84th Street
Omaha, Nebraska 68122

SEP 25 2003

Dear Dr. Augustine:

This is in response to your new dietary ingredient premarket notification dated April 28, 2003, that you submitted to the Food and Drug Administration (FDA) pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) and Title 21 of the Code of Federal Regulations (21 CFR) Part 190.6. Your initial notification, dated April 28, 2003, was amended with a new filing date of July 11, 2003. Your notification concerns the substances called "Creatine Ethyl Ester HCl" and "Creatine Ethyl Ester Bisulfate" (creatine ethyl esters) as the substances that you intend to market as new dietary ingredients in the product Cre-Ester™.

The notification informs FDA that ProNutrient Technologies, Inc. intends to market the new dietary ingredients, creatine ethyl esters, in 250 mg and 500 mg capsules or tablets under the trade name Cre-Ester™. The notification further states that "ProNutrient Technologies will also distribute Cre-Ester™ as a bulk raw material for incorporation into other nutritional supplement products." The notification states that the "recommended daily dosing of Cre-Ester™ shall be 500 milligrams to 5 grams per day, taken in a single or divided daily dose. Maximum daily exposure should not exceed 30 grams per day." The conditions of use of Cre-Ester™ as described in your notification include a statement that "Cre-Ester™ should not be used by pregnant or lactating women; individuals diagnosed with, or at risk for, renal or hepatic dysfunction; individuals taking Antabuse™ (Disulfiram); or individuals with a known hypersensitivity to any component of the product. Cre-Ester™ should not be used by children under 18 years of age, unless directed by a physician or qualified health care professional."

Under 21 U.S.C. 350b(a)(2), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

According to the information you provided in your notification, creatine esters are formed by reacting a hydrated form of creatine or anhydrous creatine with various alcohols in an acidic environment. The resultant esters are then purified by solvating in an alcohol at elevated temperatures and then cooling to form the esterifed creatine compounds.

It is not readily apparent whether the creatine esters that are the subject of your notification are "dietary ingredients" within the meaning of 21 U.S.C. 321(ff)(1) that may be lawfully used in dietary supplements. The term "dietary supplement" is defined in 21 U.S.C. 321(ff). A dietary supplement means, among other things, a "product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;
(B) a mineral;
(C) an herb or other botanical:
(D) an amino acid;
(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."

Based on the information in your submission, it is unclear that creatine ethyl esters are "dietary ingredients" within the meaning of 21 U.S.C. 321(ff)(1). Therefore, notwithstanding the discussion below of the evidence you rely upon as evidence that your products are reasonably expected to be safe, FDA cannot determine, at this time, whether your product contains a dietary ingredient that may lawfully be marketed as a dietary supplement.

Nevertheless, FDA has carefully evaluated the information in your submission and the agency has significant concerns about the evidence on which you rely to support your conclusion that creatine ethyl esters are safe for chronic human consumption. The notification submitted the results of an *in vitro* study using a mouse skeletal muscle cell line (C2C12) exposed to creatine ethyl esters at 0-100 mM for 4 hours. According to the notification, creatine ethyl esters had no effect on cell viability compared the creatine monohydrate. The notification submitted the results of an acute study in rats gavaged with 430 mg/kg/day for 7 days. According to the notification, no evidence of toxicity was observed in 8 rats gavaged with creatine ethyl esters at 430 mg/kg/day for 7 days. In addition, the notification submitted the results of a study in five adult males, dosed with 1-3 grams/day of creatine ethyl esters for 238 to 414 days. According to the notification, subject number 4 had a slightly elevated serum creatinine (1.7 mg/dL), but the albumin/creatinine ratio was normal. However, a study in five adult males dosed with different doses of creatine ethyl esters over different time periods is insufficient to establish evidence of the safe chronic human consumption of creatine ethyl esters.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that creatine ethyl esters, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable

risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of July 11, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

Susan J. Walker, M.D.
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

ProNutrient
Technologies, Inc.

11515 N. 84th Street
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Phone 402-573-6500
Fax 402-573-7646

July 17, 2003

Memo To: Vicki Lutwak
Dr. Susan Walker

From: Samuel C. Augustine, President

Subject: New Dietary Ingredient Notification – Second Supplemental Information

To further assist your review of Creatine Ethyl Ester we are submitting the following information to give you the rationale for the classification we presented in the Pre Marketing Notification.

As stated in our current notification letter, Creatine Ethyl Ester was classified under 21U.S.C.321(ff)(1)(E) "a dietary substance for use by man to supplement the diet by increasing the total dietary intake". The memo of July 11, 2003 gave a brief explanation as to our reasoning for the classification of our product as as list above. In addition we identified another category for consideration. That is 21U.S.C.321(ff)(1)(D) "an amino acid". Below is the rationale for inclusion of this category for our product.

Creatine Ethyl Ester (CreEster™) is intended to supplement the diet with creatine, a naturally occurring, recognized amino acid that is currently available to consumers, in many salt forms, as a dietary supplement. Our product is an ester modification of creatine. This modification is intended to improve the bioavailability of creatine as well as reduce gastrointestinal side effects experienced with other creatine salt forms. Our in vitro experiments support this in that when creatine ethyl ester is exposed to cultured muscle cells their creatine content is increased without demonstrable accumulation of the esterified form in the cell. Furthermore, additional experiments performed in our laboratory have demonstrated that creatine ethyl ester does not enter into the creatine kinase reaction process, thus indicating that it is the bioactivated form of creatine that is presented to and used by the muscle cell. If you need to examine the data described above, we will release it to you upon your request.

There is precedent for the use ester modifications to improve the bioavailability and decrease side effects of a supplement in the commercial market place. The example is the esterified form of vitamin C that is widely advertised and distributed throughout the United States.

Further consideration should also be given to classification of Creatine Ethyl Ester under 21U.S.C.321(ff)(1)(F) "a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);". The rationale for this is that Creatine Ethyl Ester is a combination of creatine, an amino acid, and ethanol, a GRAS material, by way of an esterification process. Again, our experiments have demonstrated that this ester form does convert to creatine and ethanol through hydrolysis of the ester bond or activity of esterases that are found throughout biological systems.

We are greatly appreciative of the opportunity to provide you with further clarification and reasoning for considering Creatine Ethyl Ester in this notification. I will be available for any questions you may have regarding this or other matters concerning this notification. I can be reached at ProNutrient Technologies (402) 573-6500, University of Nebraska Medical Center at (402) 559-5774, or my cellular (402) 680-6881. Or you may call Dr. Jon Wagner at ProNutrient Technologies or his cellular (402) 880-7124. Thank you.

ProNutrient
Technologies, Inc.

11515 N. 84th Street
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Phone 402-573-6500
Fax 402-573-7646

July 11, 2003

MEMO TO: Vicki Lutwak
Dr. Susan Walker

FROM: Samuel C. Augustine, President

SUBJECT: New Dietary Ingredient Notification – Supplemental Information

In regards to our submission of a New Dietary Ingredient Notification for Creatine Ethyl Ester we believe it meets the definition for a "new dietary ingredient" in one or more of the following categories:

Amino acid. Although not listed as an essential amino acid, creatine is technically considered an amino acid due to the fact that it is a N-methyl guanidine derivative of glycine. Creatine ethyl ester is a bio-reversible modification of creatine where the acid moiety is masked by an ester to improve water solubility. Due to this modification, creatine ethyl ester is technically an ester, but is converted to creatine and therefore, could also be considered an amino acid ester.

A dietary substance for use by man to supplement the diet by increasing the total dietary intake. Creatine is found naturally in dietary sources such as red meat, fish and milk. Creatine ethyl ester is a product intended to supplement the diet with increased creatine.

Hopefully the above information will be of value to you in reviewing our New Dietary Ingredient Notification. I will be back in the office on Monday, July 14. If you need to contact someone with ProNutrient Technologies before then, please contact Jon Wagner, Pharm.D. at 402-573-6500 (work) or 402-880-7124 (cell).

ProNutrient
Technologies, Inc.

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Friday, April 11, 2003

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835
Telephone Number: (301) 436-2371

Re: New Dietary Ingredient Notification – Creatine Ethyl Ester, (Cre-Ester™)

Please find enclosed an original and five copies of the "Notification of marketing of a new dietary ingredient – Creatine Ethyl Ester", submitted pursuant to section 413 of the Federal Food, Drug and Cosmetic Act. We wish to keep the highlighted areas of the notification as proprietary information.

This is a new submission of data recommended in the Food and Drug Administration letter to ProNutrient Technologies, Inc. of November 22, 2002. Our supplement is created through esterification of creatine, a naturally occurring amino acid, to form Creatine Ethyl Ester by reacting it with ethyl alcohol. Creatine Ethyl Ester (Cre-Ester™) is considered a dietary supplement under the definition of a dietary ingredient based upon 21U.S.C. 321 (ff)(1), (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake.

Should you have any questions regarding this notification, please contact me at 402.573.6500. Thank you for your attention to this matter.

Respectfully submitted,

Samuel C. Augustine, R.P., Pharm. D., BCNP, FAPhA
President

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COPY

New Dietary Ingredient Notification

Creatine Ethyl Ester (Cre-Ester™)